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A Rare Case of Cold Agglutinin Hemolytic Anemia Induced Gangrene

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Abstract:

Gangrene is a rare and extreme presentation of cold agglutinin disease and our case is one of only few published reports in medical literature (less than twenty). In our patient severe hemolysis as manifested by elevated indirect bilirubin, LDH and low haptoglobin was triggered by unusual infectious organisms (E. Coli and Coagulase negative Staphylococcus).

Key words: *cold agglutinin, hemolytic anemia, gangrene.*

Introduction

Cold agglutinin hemolytic anemia is a rare autoimmune hemolytic anemia secondary to antibodies that generally react with antigens on the RBC surface only at temperatures below that of the core temperature of the body. Acrocyanosis is a common finding, but gangrene is a rare presentation.

Case report:

Sixty nine year old caucasian male presented to the hospital with unresponsiveness, septic shock, hypothermia and acrocyanosis. He has a history of paranoia, cold agglutinins hemolytic anemia, and Raynaud disease for which he always wears gloves and stockings. In the ICU he had evidence of severe hemolysis with marked jaundice, elevated LDH and low haptoglobin. His acrocyanosis had progressed to intense gangrene in "stock and glove" distribution. (Figures 1 & 2) Treatment was started with passive warming, resuscitation, antibiotics, and steroids. Treatment with intravenous steroids was ineffective and cytotoxic agents were not used due to sepsis and multi system organ failure. The patient's condition continued to deteriorate with the multiple system organ failure and eventually succumbed to death.

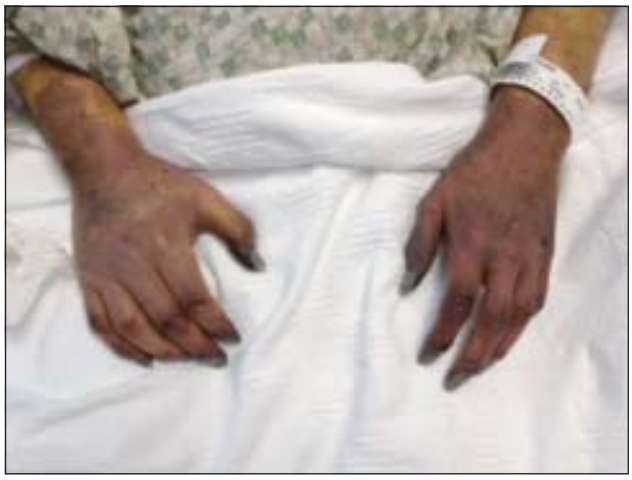

Fig.-1: *Gangrene of both hands*

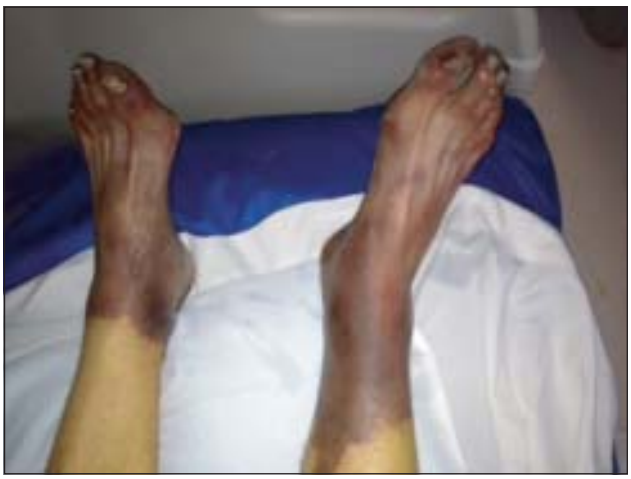

Fig.-2: *Gangrene of both feet*

Discussion:

Cold agglutinins hemolytic anemia is an autoimmune hemolytic anemia secondary to IgM antibodies that generally react with polysaccharide antigens on the RBC surface only at temperatures below that of the core temperature of the body. They are therefore called "**cold** agglutinins." Rarely, IgG antibodies have these reaction characteristics, occurring either alone or with IgM antibodies.[1] The antigens are the i antigen and the I antigen, coded by a gene on chromosome 14q. The haemolysis is due to complement fixation in the intravascular compartment, and the majority of the complement coated cells are destroyed extravascularly by the reticulo-endothelial system.[2]

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Cold agglutinin disease was first reported in animals in 1903 by Landsteiner, and first human case reported in 1918 by Clough.[3] It is a rare disease, most often affecting females in the seventh decade of life, with an incidence of one case per million people per year.[4]

Cold agglutinins are produced either in response to infection[5] or by paraneoplastic or neoplastic growth.[6] The most common infectious agents are: Mycoplasma pneumoniae, and infectious mononucleosis. Less commonly, cold agglutinins are associated with other bacterial and viral diseases, such as Cytomegalovirus, Epstein-Barr virus, Legionella, Citrobacter, Influenza, Varicella and Listeria Monocytogenes.[4,6]

Most common symptoms include anemia – 35 percent, acrocyanosis – 24 percent, fatigue – 21 percent, weakness or dyspnea on exertion – 7 percent, hemoglobinuria – 3 percent.[6] Diagnosis is made by presence of a high titer of cold agglutinins (excess of 1 in 10,000). Positive direct antiglobulin (Coombs) test for the presence of bound complement on red cells. The test is usually negative for bound IgG. The additional diagnosis of mycoplasma infection, infectious mononucleosis, or lymphoma should be made under appropriate clinical circumstances.[7] Avoidance of cold is the most beneficial therapy to prevent hemolysis. Over the years, treatment has been directed at suppressing the synthesis of the IgM monoclonal protein and has included corticosteroids, alkylating agents, azathioprine, interferon, and purine nucleoside analogues.[6,7] Recently the monoclonal anti-CD20 antibody rituximab, alone or in combination with fludarabine has shown better results than corticosteroids and alkylating agents.[8] Plasmapheresis can be used as adjunctive treatment to physically remove the IgM antibody from the plasma, leading to a reduction in the rate of hemolysis.[9]9.

Table-I

Summarizes the published reports of cold agglutinin disease associated with gangrene.

Case/Reference	Description	Outcome
Karunarathne et al.[2]2012	Cold autoimmune haemolytic anaemia secondary to Epstein Barr virus infection presenting with peripheral gangrene	Amputation, Survived
Bachmeyer C, et al.[10]2003	Raynaud's phenomenon with necrosis of the extremities induced by cold agglutinin disease secondary to a T-cell lymphoma	Died
Talisman et al. [11] 1998	Gangrene of the back, buttocks, fingers and toes caused by transient cold agglutinemia induced by a cooling blanket in a patient with sepsis	Amputation, Survived
Patel M, et al. [12]1993	Paroxysmal cold haemoglobinuria coexisting with cold agglutinins in a patient with syphilis resulting in peripheral gangrene	Survived
Freedman J, et al. [13]1985	Autoimmune hemolytic anemia with concurrence of warm and cold red cell autoantibodies and a warm hemolysin.	Survived
Poldre P, et al. [14]1985	Fulminant gangrene in transient cold agglutinemia associated with Escherichia coli infecion	Survived
Barth JH. [15] 1981	Infectious mononucleosis complicated by cold agglutinins, cold urticaria and leg ulceration.	Unknown
Jerry W, et al. [16] 1978	Cryopathic gangrene with an IgM lambda cryoprecipitating cold agglutinin	Amputations, survived
Mitchell ABS, et al. [17]1974	Cold agglutinin disease with Raynaud's Phenomenon	Survived
Kumar S, et al. [18] 1958	Symmetrical Peripheral Gangrene in Acquired Hemolytic Anemia	Unknown
Nelson MG, et al. [19] 1953	Digits gangrene with high titres of cold agglutinin	Amputations, survived
Stats D, et al. [20] 1943	Cold hemagglutination with symmetric gangrene of the tips of the extremities.	Amputations, survived

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